PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	03 AUG 2006
Applicant's or agent's file reference 38586-341002	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/43215	30 November 2005 (30.11.2005)	29 November 2004 (29.11.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC: A61K 35/32(2006.01)
USPC: 424/549

Applicant

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☒ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	18 June 2006 (18.06.2006)	Satyendra K. Singh Telephone No. 571-272-8790

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/43215

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
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Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
This International Search Authority Acknowledges applicant's claim of priority over US provisional application No. 60/631,334 filed on 29 Nov. 2004.

WRITTEN OPINION OF THE
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International application No.
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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-35	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-35	NO
Industrial applicability (IA)	Claims 1-35	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-35 meet the criteria set out in PCT Article 33(2), because the prior art does not teach or fairly suggest a composition comprising a demineralized bone matrix (DBM) having been extracted with a vhaotropic solvent, wherein the extracted DBM has osteoinductive activity, and has less non-osteogenic proteins than native DBM.

Claims 1-35 lack an inventive step under PCT Article 33(3) as being obvious over the prior art cited by the examiner as follows:
BEHNAM et al (J. Orthop. Res., 2002); URIST (US 4,789,732); SEYEDIN et al (US 4,843,063) describe the method of extracting demineralized bone matrix (DBM) using chaotropic agents such as urea or guanidinium hydrochloride under various conditions to obtain osteogenic BMPs and to extract non-collagenous proteins from the DBM preparations.
JEFFERIES (US 6,311,690 B1) and BENTZ et al (US 5,393,739) disclose the use of such DBM preparations that has been extracted with chaotropic agents in the compositions for bone repair and drug delivery along with BMP such as BMP-2 obtained from such extracts of DBM.
MILLER-BERTOGLIO et al (Dev. Biol., 1999) disclose the role of noggin as an antagonizing factor for BMP signaling during developmental stage of bone formation in vertebrates.
Therefore, it would have been obvious to a person of ordinary skill in the art at the time this invention was made to recognize the fact that DBM contains various biological factors that have antagonistic effect of bone repair (Miller et al), and the fact that the DBM extracted with chaotropic solvents such as urea or guanidinium-hydrochloride acts as a superior carrier or scaffold for bone repair (as disclosed by Jefferies; example two, in particular) when combined with osteoinductive factors, such as BMPs (as disclosed by Bentz et al). Thus, in view of the disclosures in the prior art cited by the examiner, the invention as a whole lacks an inventive step.

Claims 1-35 meet the criteria set out in PCT Article 33(4), and thus claims 1-35 have industrial applicability because the subject matter claimed can be made or used in industry.